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Surface plasmon resonance as a high throughput method to evaluate specific and non-specific binding of nanotherapeutics

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ABSTRACT

Surface plasmon resonance (SPR) is a powerful analytical technique used to quantitatively examine the interactions between various biomolecules, such as proteins and nucleic acids. The technique has been particularly useful in screening and evaluating binding affinity of novel small molecule and biomolecule-derived therapeutics for various diseases and applications including lupus medications, thrombin inhibitors, HIV protease inhibitors, DNA gyrase inhibitors and many others. Recently, there has been increasing interest in nanotherapeutics (nanoRx), due to their unique properties and potential for controlled release of encapsulated drugs and structure-specific targeting to diseased tissues. NanoRx offer the potential to solve many drug delivery challenges by enabling, specific interactions between molecules on the surface of the nanoparticle and molecules in the diseased tissue, while minimizing off-target interactions toward non-diseased tissues. These properties are largely dependent upon careful control and balance of nanoRx interactions and binding properties with tissues *in vivo*. Given the great promise of nanoRx with regard to engineering specific molecular interactions, SPR can rapidly quantify small aliquots of nanoRx formulations for desired and undesired molecular interactions. Moving forward, we believe that utilization of SPR in the screening and design of nanoRx has the potential to greatly improve the development of targeted nanoRx formulations and eventually lead to improved therapeutic efficacy. In this review, we discuss (1) the fundamental principles of SPR and basic quantitative analysis of SPR data, (2) previous applications of SPR in the study of non-particulate therapeutics and nanoRx, and (3) future opportunities for the use of SPR in the evaluation of nanoRx.

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1. Introduction to surface plasmon resonance

Surface plasmon resonance (SPR) is a powerful analytical technique that relies on changes in the refractive index at the surface of a gold chip to detect the binding of a ligand that is generally covalently fixed to the chip surface with an analyte molecule that is constantly flowing over the chip surface. Current SPR systems can detect very small (~pg/mm^2) changes in the mass of the analyte bound to the chip at a temporal resolution of approximately 0.1 s [1]. Thus, SPR is an extremely useful technique for accurately determining both equilibrium and kinetic rate constants of ligand/analyte binding events. SPR does not require any special labeling of analyte molecules, as does traditional fluorescent or radio-labeled ligand binding assays, and can be used to obtain quantitative binding parameters for analytes ranging from small molecules (~100–200 Da) to entire cells. Indeed, SPR techniques have been used to investigate binding and interactions of proteins and protein conjugates, antibodies and antibody conjugates, nucleic acids, lipid micelles, viruses, nanoparticles (NP), and cells. Further, SPR provides data in real time and, in many cases, quantitative binding data can be generated in a matter of minutes. In this section, we provide a brief overview of SPR methodology and, where appropriate, we highlight some important concepts when considering the use of SPR for nanotherapeutic (nanoRx) binding analysis.

1.1. SPR basics — device overview

A schematic of a typical SPR unit is shown in Fig. 1. Current systems generally consist of two pumps, an autosampler, a microfluidic system,

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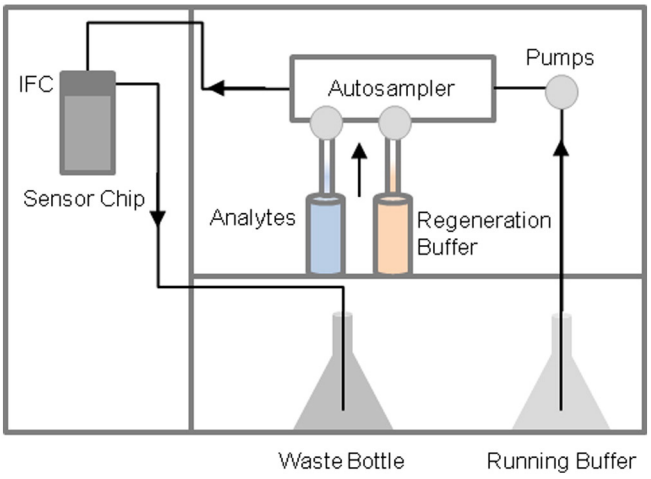

Fig. 1. Schematic of a typical SPR instrument. Arrows indicate the direction of liquid flow through the system. IFC represents the integrated microfluidic cartridge.

a detector unit, and a flow cell that is formed partially by the introduction of an interchangeable sensor chip. Generally, a sensor chip that has been covalently-modified with a ligand of interest (see Section 1.2. below for details) is docked to the machine and makes up one of the walls of the flow cell, such that buffer flow through the flow cell constantly runs across the surface of the docked chip. Analytes can then be injected into the flow cell either manually or automatically via the autosampler and a second pump system and subsequent binding events at the surface of the chip are measured by the detector as a change in refractive index at the surface of the chip. The change in refractive index is typically reported in "resonance units" or RU and this number is proportional to the mass concentration of the analyte bound at the surface of the chip. After a binding experiment, bound analyte is removed from the chip by a process called regeneration (see Section 1.4.). Typically, a single flow channel on a chip can be used for 50–100 runs with repeatable results, so long as a proper regeneration protocol and sensor chip storage procedures are in place.

1.2. The SPR sensor chip and chip preparation

A typical SPR chip consists of a glass slide that is coated with a thin layer of gold. The gold layer, in turn, is modified with various types of linker molecules and dextran depending on the type of chip/application and the desired surface chemistry required for ligand immobilization (Fig. 2). A variety of chips are commercially available for specific SPR applications, with carboxymethyl-dextran chips (specifically CM5) being most popular. Addition of ligands to the surface of the chip is achieved via either (1) covalent modification or (2) high affinity capture. As covalent modification is the most commonly used method for ligand immobilization, we will focus on this method of ligand mobilization here. Information on high affinity capture as a means for ligand immobilization can be found elsewhere [1–2].

Covalent modification of the SPR chip surface is performed via irreversible chemical reaction of ligand with amine, thiol, or aldehyde groups found in linker layers. Of the various functional groups, amine groups are the most commonly exploited for covalent conjugation of carboxyl-containing ligands to the chip surface via simple EDC/NHS chemistry. However, care must be taken to ensure the selected immobilization chemistry preserves the biochemical activity of the immobilized ligand; therefore, if vetted immobilization strategies are not available for the ligand of interest, it may be appropriate to test several immobilization chemistries to ensure maximum preservation of ligand activity.

Aside from immobilization chemistry considerations, chip selection may be particularly important for nanoRx SPR studies due to the

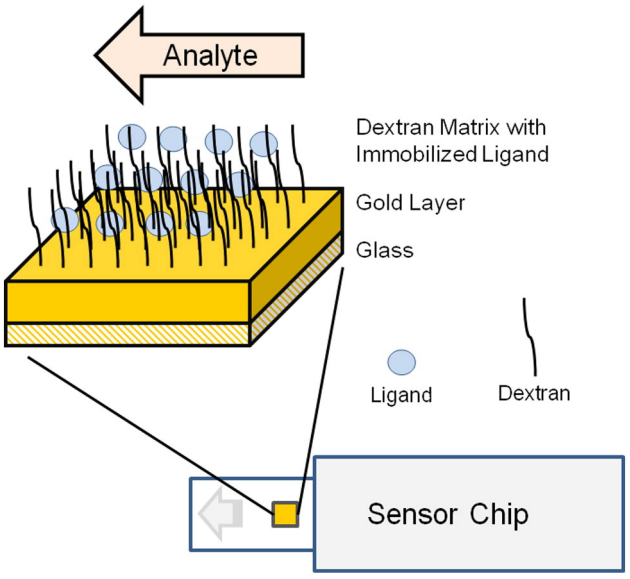

Fig. 2. Schematic of an SPR sensor chip and chip surface. Schematic shows a typical CM5 sensor chip that is surface modified with a carboxymethyl-dextran layer.

relatively larger size of nanoRx compared to more conventional SPR analytes. For instance, linker layers on SPR chips can be 10's of nm thick, giving the surface of the chip a 3-D slab type geometry. Ligand can be immobilized throughout this 3-D slab with some immobilized ligands being 10's of nm from the outermost part of the linker layer. Small conventional SPR analytes (e.g. proteins) are able to diffuse into the entangled carboxymethyl-dextran linker layer to reach the immobilized ligand in deeper layers, but larger analytes, like nanoRx, may be sterically limited from accessing all immobilized ligand. Tassa et al. observed much lower nanoRx binding (in RU) than expected from the Analyte Binding Capacity, when using a CM5 chip that utilized a carboxymethyl-dextran linker layer and hypothesized that this was due to a failure of nanoRx to penetrate fully into the linker layer and access all immobilized ligand [3]. To test this hypothesis, the authors examined the binding of nanoRx to two different chips with the same immobilized ligand. The chips were a CM5 chip and a C1 chip that lacks a dextran layer, thus providing a flatter, more 2-D like surface to eliminate issues with nanoRx penetration. The authors found that there was 15-fold more binding of nanoRx to the C1 chip than the CM5 chip, even though there was slightly less ligand immobilized to the C1 chip, supporting the hypothesis that more immobilized ligand was available to nanoRx with the C1 chip compared to the CM5 chip. However, the authors noted that more non-specific binding of nanoRx to the C1 chip was observed compared to the CM5 chip, likely due to the lack of dextran, which serves to passivate the CM5 chip surface from non-specific interactions.

In addition to ligand immobilization chemistry, the density of immobilized ligand on the chip surface is an important parameter that should be considered for experiments. In particular, it is important to immobilize sufficient ligand to ensure analyte binding results in measurable changes in RU. This is most important for low molecular weight analytes that contribute a relatively small mass increase at the chip surface for each binding event. Current SPR machines allow the user to set the level of immobilized ligand in RU during immobilization reaction procedures. Methods for selecting appropriate ligand immobilization densities can be found elsewhere [2]. An additional consideration in the case of nanoRx, the focus of this review, is the selection of ligand densities (e.g. in pmol/nm^2) that correspond to physiologic densities on target cells and tissues. Using relevant ligand densities can give SPR experiments physiologic meaning in addition to providing a quantitative measure to assess nanoRx binding characteristics. This point is discussed further in Section 4.3.

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